

22
66. (amended)

20 21
63 or 64 [65]

The pharmaceutical composition of claim ~~63~~ or ~~64~~ [65],
wherein said compound is present in an amount effective to inhibit the proteasome function in
a mammal.

Ab
Carter

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2, 3, 5, 6, 11-24, 43-50, 63-66 and 90-94 are pending in the application, with claims 90, 93, 94, 24 and 43 being the independent claims. Claims 1, 4, 7-10, 25-42, 51-62 and 67-89 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to file one or more divisional applications on the subject matter encompassed by the canceled claims. New claims 90-94 are sought to be added.

Claim 1 was canceled and replaced with new claim 90. The limitations of claims 1, 4, 7 and 10 have been included in new claim 90. Thus, B² has been limited to an amide linkage. The subscript "A" has been limited to zero (eliminating coverage of tri- and tetra- peptide derivatives, and the corresponding X¹, R¹ and B¹ groups). Optional substituents for R², R³ and R⁵ members have been defined. Support for the added limitations occurs at page 18, lines 13-21 of the description. "Alkyl" has been deleted from the Z¹ and Z² expressions. The member "a 5-10 membered saturated, partially unsaturated or aromatic heterocycle" in the Markush expressions of R², R³ and R⁵ have been deleted in response to the Examiner's election of species requirement to expedite allowance of the present application. Deletion of individual members of a Markush expression does not constitute new matter. See, *In re*

Johnson and Farnham, 194 USPQ 187 (CCPA 1977). The limitations "quinolinyl, pyridyl, indolyl" have been included to further define the heterocyclic groups of the R⁵ expression. Support for this change occurs at page 18, lines 22-29 of the description.

Claim 91 is similar to claim 21, except that the R² group in claim 91 cannot include a heteroaryl ring. Claim 92 limits the P group of claim 91 to 2-pyrazinecarbonyl, 8-quinolinesulfonyl or N-morpholinoyl. Claim 93 is directed to the generic concept identified by the Examiner except that cyclic esters of the boronic acid have been retained within the scope of the claim.

Claim 94 is directed to a preferred embodiment of the invention defined by claims 43-50.

Claim 12 was amended to define optional substituents for R², R³ and R⁵ members and to delete "a 5-10 membered saturated, partially unsaturated or aromatic heterocycle" in the Markush expressions of R², R³ and R⁵. In claims 17 and 22, the group 4-(2'-pyridylmethoxy)benzyl has been deleted from the Markush expression for R². The groups 3-pyridylmethyl, 2-pyridylmethyl, 6-quinolinylmethyl and 3-indolylmethyl groups presently remain in the R² expression. Claim 24, directed to the elected species, has been changed to an independent claim. The remaining claims have been amended to be consistent with the changes discussed above, or to update dependency of the claims.

Applicants reserve the right to prosecute the canceled subject matter in one or more divisional applications. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above Amendment and the following Remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the outstanding objection.

I. Restriction Requirement

Applicants elected the compound N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid in response to the election of species requirement. The Examiner has treated the election of species requirement as a restriction requirement. The Examiner has "identified" a generic concept inclusive of the elected species for examination. This generic concept is directed to compounds of claim 1 where P is pyrazinecarbonyl, R is H or alkyl, A is zero, R² and R³ are hydrogen, alkyl, cycloalkyl, aryl, or -CH₂-R⁵, where the ring portion of any of said aryl, aralkyl, or alkaryl can be optionally substituted by non-heterocyclic groups; R⁵ is one of aryl, aralkyl, alkenyl (*sic*, alkaryl, cycloalkyl, or -W-R⁶, where W is a chalcogen and R⁶ is alkyl), each optionally substituted by non-heterocyclic groups; Z¹ and Z² are hydroxy, alkoxy, or aryloxy, and pharmaceutically acceptable salts thereof.

The remaining subject matter, whether included in claim 1 or not, has been withdrawn from consideration as constituting other patentably distinct inventions. With respect to compounds, the Examiner stated that subject matter differs in structure and element so as to be patentably distinct therefrom. Claims 67-89 were withdrawn as being directed to a patentably distinct, different statutory category of invention.

The restriction between methods of using (claims 67-89) and compositions of matter (claims 1-66) amounts to a new restriction requirement. To this extent, Applicants confirm that they desire to prosecute the invention of claims 1-66.

Applicants traverse to the extent that the election of species requirement as between compounds is deemed to be a restriction requirement, and/or to the extent that examination is not conducted pursuant to the guidelines set forth at MPEP § 803.02. Notwithstanding

current PTO policy, restriction practice is *not* applicable to a single claim. See, *In re Weber*, 198 USPQ 332 (CCPA 1978) and its companion case, *In re Haas*, 198 USPQ 334 (CCPA 1978). These cases make it clear that 35 U.S.C. § 121 does not grant to the PTO the authority to refuse to examine a single claimed invention. Section 121 only applies to *plural* claimed inventions in *different* claims, wherein the different claims vary not just in scope, but in the invention to which each is directed.

Applicants submit that search and examination of the entire scope of the amended claims would not pose a serious burden to the Examiner or the PTO, despite the different classifications that result from the inclusion of a reasonable number of heterocyclic Markush group members. The potential burden to Applicants of prosecuting and maintaining patents for each heterocyclic group that can appear at P or R²/R³ would be enormous.

Reconsideration of the Examiner's position, and consideration and allowance of all pending claims, are respectfully requested.

II. Objection to Claims: Inclusion of Non-Elected Subject Matter

The Examiner objected to claims 1-7, 11-19, 21-24, 25-27, 29, 30, 43-45, 47-49, 51-53, 55, 57, 63 and 66 for allegedly containing non-elected subject matter. Applicants traverse.

In making a "restriction requirement" within the objected claims, the Examiner relied upon the rationale that a reference anticipating one species within the Markush group will not render obvious another species within the Markush group; and that compounds within the claims were classified differently. The test for proper joinder of invention within a claim is

not whether a reference anticipating one species will render obvious another species within the Markush group. Rather, unity of invention is the proper analysis. Unity of invention exists for compounds when the compounds share a common structural core and share a community or properties, such that the grouping of such compounds together is not repugnant to principles of scientific classification. See *In re Harnisch*, 206 USPQ 300, 305 (CCPA 1980). Neither is different classification is a sufficient condition to require restriction.

Applicants elected the compound N-(2-pyrazine)carbonyl-L-phenylalanine-L-leucine boronic acid pursuant to a written election of species requirement. The claims, as currently amended, are directed to compounds that share a common core or nucleus, namely a dipeptide backbone, wherein the C-terminal carboxyl group is replaced with a boronic acid, or esters (cyclic or acyclic) thereof, and the terminal nitrogen is covalently attached to a heterocyclecarbonyl or heterocyclesulfonyl group, where said heterocycle is selected from the group consisting of quinolinyl, quinoxalinyl, pyridyl, pyrazinyl, furanyl, pyrrolyl or morpholinyl. The compounds share a common function, namely inhibiting proteosome activity.

Applicants request the Examiner to reconsider and withdraw the objection to the claims in view of Applicants' amendments.

III. Indication of Allowable Subject Matter

The indication of allowable subject matter is noted and appreciated by Applicants.

IV. Other Matters - Consideration of All Documents Cited on PTO-1449

A number of documents cited on the 9 sheets of PTO Form 1449 were not considered by the Examiner on the basis that copies of the documents were not provided.

No copies were provided for a number of documents that were cited in parent application, serial no. 08/442,581. The Information Disclosure Statement referenced the earlier filed application. Applicants appreciate that the file was not readily accessible to the Examiner at the time of examination. However, the parent application file is now in Art Unit 1201 with Examiner Lutz. As copies of the relevant documents appear in the parent application, Applicants respectfully request that the Examiner indicate consideration of these documents. If an additional set of copies will assist the Examiner, he is invited to call the undersigned representative who will forward such copies. Copies of the original nine sheets of Form PTO-1449 are attached hereto.

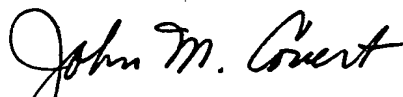
V. Conclusion

The stated grounds of objection has been properly traversed, accommodated or rendered moot. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, she is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

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